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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MARSHALL O'TOOLE GERSTEIN
MURRAY & BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 606066402

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/224,683	ZSEBO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 71-114 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection of claims 71-114 under 35 U.S.C. § 112, second paragraph at pg 11-12 of the previous Office Action (Paper No. 9, 20 July 2001) is *withdrawn* in part in view of Applicant's persuasive arguments (Paper No. 10, 29 January 2002). Please see section on 35 U.S.C. § 112, second paragraph below.

Double Patenting

2. The rejection of claims 71-114 under obviousness-type double patenting at pg 2-4 of the previous Office Action (Paper No. 9, 20 July 2001) is maintained and held in abeyance until an executed terminal disclaimer is filed.

Specification

3. The objection to the specification regarding sequence compliance, priority, the Brief Description of Drawings, and references to other patent applications is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit the appropriate corrections at Applicant's earliest convenience so that the Examiner can approve of the corrections.

Claim Objections

4. The objection to claim 104 regarding a missing "." at the end of the claim is maintained and held in abeyance. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition which comprises an effective amount of *human* stem cell factor (SCF) polypeptide and one or more cytokines in a pharmaceutically acceptable carrier wherein the SCF composition enhances hematopoiesis, does not reasonably provide enablement for a composition which comprises a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat hematopoietic disorders, epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders. Further, the specification, while being enabling for the SCF polypeptide consisting of the amino acid sequence of 1-162, 1-164, 1-165 of SEQ ID NO: 46; 1-130, 1-137, 1-248, 2-164, 5-164, 11-164 of SEQ ID NO: 61; and 1-220 of SEQ ID NO: 63, does not reasonably provide enablement for the SCF polypeptide consisting of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 as set out in Figures 42A-C and 44A-C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 5-9 of the previous Office Action (Paper No. 9, 20 July 2001).

Applicant's arguments (Paper No. 11, 29 January 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that one of skill in the art, in view of the teachings of the specification, and in view of the state of the art at the time the application was filed, would be able to practice the invention encompassed by the claims without undue experimentation. Applicant argues that the enablement requirement is satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. Applicant cites *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973) to emphasize that the above enablement clause does not require a specific example of everything within the scope of a broad claim. Applicant contends that that the invention of the instant application has been defined in terms of structure and function. Applicant argues that the examiner admits the specification teaches a SCF polypeptide and fragments thereof. Applicant also states that regarding function, the disclosed SCF polypeptides have been defined by their expression and their association/use in many disease states.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification does not teach all analogs or variants of the SCF polypeptide of the instant application. The specification only teaches that the human SCF polypeptide, particularly fragments comprising amino acids 1-130, 1-137, 1-162, 1-164, 1-165, 1-220, 1-248, 2-164, 5-164, and 11-164 of SEQ ID NOs: 46, 61, and 63, enhance the proliferation and differentiation of bone marrow progenitor cells (pg 108-114, 170-178, 185). The specification does not disclose any methods or working examples to indicate that human SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158,

1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63 or any variants or "analogs" have any specific activity. A large quantity of experimentation would be required of the skilled artisan to determine any structural or functional characteristics of the SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63. These particular SCF fragments identified by the examiner to be non-enabled have not been defined by their expression or their association/use in many disease states. The specification at pg 17-31 discloses many prophetic examples in which SCF polypeptides and/or biologically active fragments could be useful to treat disease. However, the structure and function of every SCF fragment and analog claimed is not disclosed in a manner such that one skilled in the art could make and use them without undue experimentation.

Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily be able to generate the infinite number of SCF derivatives recited in the claims and screen the same for activity.

(ii) Applicant asserts that given the amount of guidance in the specification and high level of skill in the biotechnology art, the skilled artisan would readily and easily be able to make and use the biologically active variants, analogs, and fragments of SCF polypeptides without undue experimentation. Applicant also contends that the specification discloses that biologically active variants, analogs, and fragments of SCF polypeptides, wherein one or more nucleotides and/or amino acids are designed to differ from the wild-type or naturally occurring SCF, can be produced using techniques that are well known in the art.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins,

this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of SCF derivatives recited in the claims and to screen them for a desired activity. Such trial and error is considered undue. Therefore, one skilled in the art cannot predict that the human SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63 or any variants or "analogs" of the instant application will have the same functional activities as the human SCF fragments comprising 1-162, 1-164, 1-165 of SEQ ID NO: 46; 1-130, 1-137, 1-248, 2-164, 5-164, 11-164 of SEQ ID NO: 61; and 1-220 of SEQ ID NO: 63, since deletions of amino acid residues can often destroy activity of a protein.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the "biologically active" derivatives or "analogs" recited in the claims, to determine the specific activity of a polypeptide fragment, and to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding which structural features that are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 9-11 of the previous Office Action (Paper No. 9, 20 July 2001).

Claims 71-114 recite a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat hematopoietic disorders, epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders. The claims also recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 as set out in Figures 42A-C and 44A-C.

Applicant's arguments (Paper No. 11, 29 January 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that there is no requirement in patent law that every species within a 'genus' claims be disclosed. Applicant cites *In re Grimme, Keil and Schmitz* 124 USPQ 499, 502 (CCPA 1960) to emphasize that it is impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every species.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification does not teach all analogs or variants of the SCF polypeptide of the

instant application. Regarding *In re Grimme, Keil, and Schmitz*, the claimed compounds formed a subgenus under the genus sufficiently disclosed in the parent application. The specification of the parent application pointed out that piperidino salts form a definite part of applicants' generic invention, and gave one example of such a compound together with a number of other examples of compounds included in the genus. Since instant piperidino compounds do not differ radically from each other or from compounds claimed in the parent patent, the examples were adequate to show those skilled in art how invention of subgenus claims is to be practiced.

However, the court also held that:

> "naming of one member of such a group is not, in itself, proper basis for claim to entire group; however, it may not be necessary to enumerate plurality of species if genus is sufficiently identified in application by other appropriate language; what constitutes such language depends on circumstances of each case; where claimed group involves compounds which differ radically from each other, it may not be sufficient to identify group broadly and to name one or two compounds falling within it." *In re Grimme, Keil, and Schmitz* 124 USPQ 499, 502 (CCPA 1960)

In the instant application, the description of ten specific SCF polypeptide fragments that enhance hematopoiesis is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all biologically active fragments and analogs of SCF. As discussed in the previous Office Action at pg 7-8, structurally similar proteins may have different functions. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Therefore, one skilled in the art cannot predict the functional activities of every SCF

analog or variant recited in the claims. With the exception of the SCF polypeptide consisting of the amino acid sequence of 1-162, 1-164, 1-165 of SEQ ID NO: 46; 1-130, 1-137, 1-248, 2-164, 5-164, 11-164 of SEQ ID NO: 61; and 1-220 of SEQ ID NO: 63, the skilled artisan cannot envision the detailed structure and function of the all possible SCF polypeptide fragments and analogs encompassed by the claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

35 USC § 112, second paragraph

7. Claims 71-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at pg 11-12 of the previous Office Action (Paper No. 9, 20 July 2001).

8. Regarding claims 91-102, the acronyms "IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Applicant's arguments (Paper No. 11, 29 January 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that with respect to use of cytokine abbreviations, such abbreviations are art-recognized abbreviations and as such are neither vague nor indefinite.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, abbreviations are less clear then the actual terms being abbreviated.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BEB
Art Unit 1647
March 13, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER